REMARKS

I. Status of the claims

Applicants have added new claims 10-18. The currently pending claims are 1-4 and 6-18. In addition, certain compounds have been deleted from claim 8. Claim 3 has been amended to remove the compound MK-886 which was erroneously included. The examiner withdrew claim 5 pursuant to an election of species requirement in Paper No. 7. As stated in Paper No. 7, applicants will be entitled to reconsideration of claims such as claim 5 which depend from any claims eventually allowed.

Support for the specific leukotriene B_4 receptor antagonists in claims 10-12 can be found on page 8, line 26 through page 9, line 5 of the specification. Support for the specific cyclooxygenase-2 selective inhibitors in claims 13-15 can be found on page 11, line 14 through page 17, line 26 of the specification. Support for the inhibitor of claim 13 is at page 12, line 7. Support for the inhibitor of claim 14 is at page 16, line 17. Support for the inhibitor of claim 15 is at page 17, line 36. Support for the pharmaceutically-acceptable salts thereof in claims 13-15 is at page 11, line 12. Support for the combination in claim 16 is in Examples 3 (p. 43) and 5 (p. 45). Support for the combination of claims 17 and 18 is in the text bridging pages 7 and 8.

Applicants note that the rejections A-D under section 112, second paragraph, and the enablement rejections, have been withdrawn.

II. 35 U.S.C.112, First Paragraph Rejections

A. *Claims 1-2 and 6-9 satisfy the written description requirement*

Reconsideration is requested of the rejection of claims 1-2 and 6-9 under 35 U.S.C. §112, first paragraph, as stated on page 3 of the Office action. This was stated to be a written description rejection. Applicants note that claims 1-2 and 6-9 are of varying scope, and request that their compliance with the written description requirement be evaluated separately.

The PTO "Written Description Guidelines" quoted in the Office action state at 1242 OG 172, citing the *Vas-Cath* case, that "To satisfy the written description

requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor has possession of the claimed invention." This can be accomplished in a variety of alternative ways, as further stated in the "Written Description Guidelines" (and MPEP):

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The Written Guidelines also state:

> An applicant may show possession of an invention by disclosure of ... structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the invention as a whole. The description need only describe in detail that which is new or not conventional. Guidelines 1242 OG 173.

The foregoing refers to a footnote 40 which recites the following from *Eli Lilly*, 43 USPQ2d at 1406:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus.

Accordingly, written description can be satisfied by any of the methods in the following non-exhaustive list:

> 1. By sufficient description of a representative number of species by actual reduction to practice;
>
> 2. By sufficient description of a representative number of species by actual reduction to drawings;

3. By sufficient description of a representative number of species by disclosure of relevant structural chemical formulas;

4. By sufficient description of a representative number of species by disclosure of relevant, identifying characteristics, i.e, other physical and/or chemical properties;

5. By sufficient description of a representative number of species by functional characteristics coupled with a known or disclosed correlation between function and structure; or

6. By sufficient description of a representative number of species by a combination of such identifying characteristics.

In the present application, applicants "describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventors had possession of the claimed invention" because they provide sufficient description of a representative number of species by disclosure of relevant structural chemical formulas.

With regard to claim 1, it is directed toward a **combination** comprising two **known** compounds, an LTB_4 receptor antagonist and a Cox-2 inhibitor, and claims both compounds functionally in terms of their selectivity. The compounds are known, as emphasized in the specification at page 2, line 34 through page 3, line 8:

> Compounds which selectively inhibit cyclooxygenase-2 have been described in U.S. patents 5,380,738, 5,344,991, 5,393,790, 5,466,823, 5,434,178, 5,474,995, 5,510,368 and WO documents WO96/06840, WO96/03388, WO96/03387, WO95/15316, WO94/15932, WO94/27980, WO95/00501, WO94/13635, WO94/20480, and WO94/26731.
>
> Compounds which affect leukotriene B_4 have been described. U.S. Patent No. 5,384,318 describes substituted sulfonamides for the treatment of asthma. U.S. Patent No. 5,246,965 describes aryl ethers as leukotriene B_4 receptor antagonists.

Not only are the compounds well known, the specification provides over 100 examples of **specific compounds** that selectively inhibit cyclooxygenase-2[1] and over

[1]See pages 5-6 and 11-18 of the specification.

40 examples of **specific compounds** that are selective leukotriene B_4 receptor antagonist.[2] Relevant structural chemical formulas are therefore provided for a representative number of species. In addition, the specification provides a detailed definition regarding exactly what constitutes a "selective" cyclooxygenase-2 inhibitor and a "selective" leukotriene B_4 receptor antagonist:

> ...compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Preferably, the compounds have a cyclooxygenase-2 IC_{50} of less than about 0.5 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC_{50} of greater than about 1 μM and more preferably of greater than 20 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.
>
> ...compounds which selectively antagonize a leukotriene B_4 receptor with an IC_{50} of less than about 10 μM. More preferably, the leukotriene B_4 receptor antagonists have an IC_{50} of less than about 1 μM.

In re Herschler[3] is instructive, wherein the inventor claimed a combination comprising dimethyl sulfoxide (DMSO) and "a physiologically active steroidal agent" as follows:

> Claim 1: A method of enhancing the penetration into and across an external membrane barrier of a human or animal subject of a physiologically active steroidal agent capable of eliciting a physiological effect upon topical application thereof, which comprises the concurrent topical administration to the external membrane of an amount of said steroidal agent effective to produce the desired physiological effect and an amount of DMSO sufficient to effectively enhance penetration of said steroidal agent to achieve the desired physiological effect.

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[2]See pages 8-9 of the specification.

[3]In re Herschler, 591 F.2d 695, 200 USPQ 711 (1979).

Similar to the present Office action, it had been urged "that the class of steroids is so large that a single example in the specification could not describe the varied members with their varied properties."[4] The CCPA reversed the rejection, holding that "the **use of known** chemical compounds in a manner auxiliary to the invention must have a corresponding written description **only so specific as to lead one having ordinary skill in the art to that class of compounds**."[5]

Similar to the combination of *In re Herschler*, claim 1 is directed to a composition employing the use of **two known classes** of chemical compounds: cyclooxygenase-2 selective inhibitors and selective leukotriene B_4 receptor antagonists. As a class, "selectivity" is defined functionally in the specification for both cyclooxygenase-2 inhibitors and leukotriene B_4 receptor antagonists as quoted above such that a skilled artisan can readily distinguish members that belong to each class from those that do not (i.e. a "selective" compound from a non-selective compound) based upon the function of the particular compound irrespective of the chemistry it may possess. Moreover, in *In re Herschler,* claims were directed to "a physiologically active steroidal agent" as a class of chemical compounds where the specification detailed **only 1 example**. In the instant case, the specification provides over 100 specific examples of compounds that selectively inhibit cyclooxygenase-2 and over 40 specific examples of compounds that are selective leukotriene B_4 receptor antagonist, thus providing relevant structural chemical formulas for a representative number of species. If the CCPA determined that a functional description and one example satisfied the written description requirement, applicants' functional description plus 100 and 40 examples which have the respective common attribute required in the claim, namely, selectivity for cyclooxygenase-2 and leukotriene B_4 antagonist selectivity, respectively cannot fairly be deemed to be a insufficient description.

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[4]Id at 701.

[5]Id at 702 (emphasis added).

In another situation analogous to the present one, *In re Fuetterer*, the inventor claimed a composition for use in the production of rubber tires where one component of the composition was described **only functionally** as an "inorganic salt that is capable of holding a mixture of said protein and/or carbohydrate in colloidal suspension." The CCPA reversed a rejection, holding that it is permissible to use only terms of effect or result to the extent that the terms accurately describe essential qualities of a product to one skilled in the art.[6] According to the court, the essential qualities of the inorganic salt were sufficiently described solely by its ability to maintain other components of the composition in "colloidal suspension"[7]:

> Appellant's invention is the *combination* claimed and not the discovery that certain inorganic salts have colloid suspending properties. We see nothing in patent law which requires appellant to discover which of all those salts have such properties and which will function properly in this combination. The invention description clearly indicates that any inorganic salt which has such properties is usable in his combination. If others in the future discover what inorganic salts additional to those enumerated do have such properties, it is clear appellant will have no control over them per se, and equally clear his claims should not be so restricted that they can be avoided merely by using some inorganic salt not named by appellant in his disclosure. The only "undue burden" which is apparent to us in the instant case is that which the Patent Office has attemptee to place on the appellant. The Patent Office would require him to do research on the "literally thousands" of inorganic salts and determine which of these are suitable for incorporation into his claimed combination, apparently forgetting that he has not invented, and is not claiming, colloid suspending agents but tire tread stock composed of a combination of rubber and other ingredients.

Analogous to *In re Fuetterer,* the LTB applicants' invention is a *combination*, and the LTB applicants are not claiming LTB_4 antagonists nor Cox-2 inhibitors. Claim 1 describes "essential qualities" of each component of the combination to a skilled artisan. Both the cyclooxygenase-2 inhibitor and the leukotriene B_4 receptor antagonist

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[6] Id 259 F2d at 264.

[7] Id at 265.

are identified in claim 1 by their ability to either **selectively** inhibit a particular enzyme or **selectively** function as a receptor antagonist, just as the inorganic salt in *In re Fuetterer* was described solely by its ability to maintain other components of the composition in "colloidal suspension."[8] This selectivity is described in detail in the above-quoted passages from the specification. Moreover, the Written Description Guidelines are satisfied because applicants provide relevant structural chemical formulas for a representative number of species.

Significantly, the Written Guidelines specifically state "The description need only describe in detail that which is new or not conventional." 1242 OG 173. Cyclooxygenase-2 selective inhibitors are not new. Selective leukotriene B_4 receptor antagonists are not new.

In sharp contrast to the present situation, the *Enzo Biochem* case cited in the Office action involved a claim for a single **unknown** compound, not two **known** compounds in combination:

> Claim 1. A composition of matter that is specific for Neisseria gonorrhoeae comprising at least one nucleotide sequence for which the ratio of the amount of said sequence which hybridizes to chromosomal DNA of Neisseria gonorrhoeae to the amount of said sequence which hybridizes to chromosomal DNA of Neisseria meningitidis is greater than about five, said ratio being obtained by a method comprising the following steps .... (U.S. Pat. 4,900,659).

The patentee in *Enzo Biochem* was essentially claiming a result – a particular binding activity – without telling the public what achieves that result or establishing that it had possession of what achieved that result.

The Office also cites the *University of California v. Eli Lilly and Co*[9] to support its assertion that a "skilled artisan would [not] recognize Applicants were in possession of

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[8]While *Fuetterer* does not contain claims to Cox-2 inhibitors or LTB_4 inhibitors, it does not need to. It is the legal principles contained within a case that serve as precedent and not the facts of the individual case.

[9]*University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398.

the claimed combination." While *Eli Lilly* may state the law correctly, its facts are so distinct from the present situation that it is readily distinguishable. *Eli Lilly* pertains to written description requirements when the invention is directed to claims to nucleic acid and amino acid sequences, which include **unknown and unpredictable sequences**. Specifically, this case addresses the adequacy of written description when claims are directed toward genetic material, namely, cDNA sequences employed in both constructs and microorganisms. The compounds in the present application are not unknown and unpredictable genetic material, they are **known compounds**. And in *Eli Lilly*, the sequences were being claimed *per se*; but in the present case the compounds are not being claimed *per se*. In fact, the most relevant portion of the *Eli Lilly* Court's opinion to the present situation is its statement, at 116 F.2d 1568:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus.

The court goes on to contrast chemical materials with the genetic materials at issue: "In claims to genetic material, however, ..."

Applicants respectfully submit, therefore, that they have adequately demonstrated possession of the invention of claim 1 because i) they provide relevant structural chemical formulas for a representative number of species, ii) they provide a detailed definition of what constitutes a "selective" cyclooxygenase-2 inhibitor and a "selective" leukotriene B_4 receptor antagonist, iii) claim 1 is directed to a combination of two known compounds, and iv) the foregoing satisfies the written description requirements as stated in the Guidelines as supported by *Eli Lilly*.

With regard to claims 2, 6, 7, and 9, they are directed toward a **combination** of two **specific** compounds: an LTB_4 receptor antagonist described functionally, and a Cox-2 inhibitor described structurally. Applicants establish possession of the invention of these claims for the same reasons as claim 1, and because the specification provides a) identifying structure for more than 40 LTB4 receptor antagonists within the

scope of the claim, and b) the verbatim "structural chemical formula" for the Cox-2 inhibitor of the claim.

With regard to claim 8, it is directed toward a **combination** of two **known** compounds: an LTB_4 receptor antagonist described structurally, and a Cox-2 inhibitor described structurally. Applicants establish possession of the invention of this claim for the same reasons as claim 1, and because the specification provides a) identifying verbatim structure for every one of the roughly 35 LTB4 receptor antagonists within the scope of the claim, and b) the verbatim structural chemical formula for the Cox-2 inhibitor of the claim.

Applicants respectfully take issue with the assertion in the Office action that the case *University of Rochester v. G.D. Searle & Co., Inc.*[10] is more on point than the other cases because this case deals with Cox-2 inhibitors. The *Rochester* situation was fundamentally distinct from the present situation because in *Rochester* the specification reflected no knowledge whatsoever of the names of specific compounds which would work, whereas in the present situation both compounds in the applicants' claimed combination are well known, and the applicants provide an abundant list of specific compounds that work. The issue before the *Rochester* court was stated as follows:

> ...the real issue here is simply whether a written description of a claimed method of treatment is adequate where a compound that is necessary to practice that method is described only in terms of its function, and where the only means provided for finding such a compound is essentially a trial-and-error process.

The court characterized the specification as doing "no more than describ[ing] the desired function of the compound called for .... At best, it simply indicates that one should run tests on a wide spectrum of compounds in the hope that at least one of them will work"; a conclusion based on the following findings by the court in *Rochester*:

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[10] *University of Rochester v. G.D. Searle & Co., Inc.*, 249 F. Supp. 2d 216.

> Nowhere ... does it specify *which* "peptides, polynucleotides, and small organic molecules" to identify those that inhibit the expression or activity of the PGHS-2 gene product....
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> The patent describes in detail the screening assay ... but it does not identify any particular drugs that the assay will identify as suitable for this purpose.
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> Section 5.7 captioned "compounds identified in the screens," which might be expected to state which compounds had been identified...[did not].... There is no indication that the inventors themselves had identified any such compounds from among those listed., however.
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> In none of these descriptions, then, is there even any suggestion that the inventors had identified so much as one compound that would be suitable for use in practicing the claimed invention.

Inasmuch as applicants' specification provides over 100 examples of specific compounds that selectively inhibit cyclooxygenase-2 and over 40 examples of specific compounds that are selective leukotriene B_4 receptor antagonist, the *Rochester* case is inapposite.

With regard to the assertion in the Office action that the specification fails to show possession of the invention since "the disclosure fails to describe the common attributes or characteristics that identify ***all*** of the members of the genus or even a substantial portion thereof ..." (emphasis in original), applicants respectfully submit that there is no requirement, statutory or otherwise, to describe the common attributes or characteristics that identify all or a substantial portion of a genus. While describing such common attributes may be one way to establish possession of the invention, it is not the only way. Applicants establish possession of the invention by disclosure of relevant structural chemical formulas, as specifically contemplated in the Guidelines and *Eli Lilly* , and therefore need not establish possession by description of common attributes.

With regard to the assertion in the Office action that "...Applicant must provide some correlation between the structure and function of the claimed compounds...," applicants respectfully submit that there is no requirement, statutory or otherwise, to

provide some correlation between the structure and function of the claimed compounds. While describing such a correlation may be one way to establish possession of the invention, it is not the only way. In fact, for many inventions there is no known correlation between function and structure. In Comment 22 on the Written Description Guidelines at 1242 OG 171, the Office specifically stated "An inventor does not need to know how or why the invention works in order to obtain a patent." Comparing the specification to the claims in evaluating sufficiency of written description, applicants emphasize that the standard is not whether applicants have explained a correlation between structure and function, nor is it whether every species is enabled; the standard is whether the applicants have "described the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." Applicants establish possession of the invention by disclosure of relevant structural chemical formulas, as specifically contemplated in the Guidelines and *Eli Lilly* , and therefore need not establish possession by establishing a correlation between the structure and function.

Applicants therefore respectfully submit that they have demonstrated possession of the invention as claimed because i) they provide relevant structural chemical formulas for a representative number of species, ii) they provide a detailed definition of what constitutes a "selective" cyclooxygenase-2 inhibitor and a "selective" leukotriene B_4 receptor antagonist, iii) the claims are directed to combinations of two known compounds, and iv) the foregoing satisfies the written description requirements as stated in the Guidelines as supported by *Eli Lilly*.

B. *Claim 8 does not contain new matter*

Claim 8, amended in the March 19, 2003 Response stands rejected for failure to show support in the specification for newly added compounds. Support for the compounds added in amended claim 8 can be found in the specification, from page 11, line 14 to page 17, line 26. In addition, any compound not contained within the specification has been deleted. As a result, claim 8 contains no new matter and the

basis for this rejection, therefore, has been removed. Applicants respectfully request the withdrawal of the 35 U.S.C. 112, First Paragraph rejection.

III. 35 U.S.C.112, Second Paragraph Rejection

Reconsideration is requested of the rejection of claims 1-4 and 6-9 under 35 U.S.C. §112, second paragraph. These claims were rejected on the basis that they are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Office has rejected claims 1-4 and 6-9 for failing to set forth the conditions under which the "selective activity" of the claimed selective cyclooxygenase-2 inhibitors and selective leukotriene B_4 antagonists is to be measured, thus precluding a determination of the "metes and bounds" of the claimed invention.

Applicants have defined selective cyclooxygenase-2 inhibitors as:

> . . .compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Preferably, the compounds have a cyclooxygenase-2 IC_{50} of less than about 0.5 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC_{50} of greater than about 1 μM and more preferably of greater than 20 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID induced side effects.[11]

Furthermore applicants have defined selective leukotriene B_4 antagonists as:

> . . . compounds which selectively antagonize a leukotriene B_4 receptor with an IC_{50} of less than about 10 μM. More preferably, the leukotriene B_4 receptor antagonists have an IC_{50} of less than about 1 μM.[12]

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[11] Specification, page 7, line 29 to page 8, line 2.

[12] Specification page 8, lines 3-7.

Thus, applicants have disclosed a binding assay and the ranges of binding affinity which can be employed to indicate which compounds fall within the classification of either a selective cyclooxygenase-2 inhibitor or a selective leukotriene B_4 antagonist. Moreover, the specification provides over 100 examples of specific compounds that selectively inhibit cyclooxygenase-2[13] and over 40 examples of specific compounds that are selective leukotriene B_4 receptor antagonist.[14]

MPEP 2173.02 requires that definiteness of a claim be analyzed in light of the disclosure of the instant application, the teachings of the prior art, and the claim interpretation that would be given by one of ordinary skill in the art at the time the invention was made. Analyzed in this light, the required "selective activity" does not render the claims indefinite, and these claims satisfy the requirements of §112, second paragraph.

In light of the comprehensive disclosure found in the specification, the claims directed to a combination comprising a selective cyclooxygenase-2 inhibitor and a selective leukotriene B_4 antagonist are not indefinite and meet the requirements of 35 U.S.C. 112, Second Paragraph.

IV. 35 U.S.C.102 Rejection

Reconsideration is requested of the rejection of claim 1 under § 102(b) or (e) as anticipated by Buchmann et al.

Buchmann et al. generally disclose a class of compounds that are leukotriene B_4 receptor antagonists, and that their leukotriene B_4 receptor antagonists may be combined with one of several classes of compounds, one of which is a cyclooxygenase inhibitor. In contrast, claim 1 is directed toward a combination comprising a cyclooxygenase-2 **selective** inhibitor and a selective leukotriene B_4 receptor antagonist.

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[13]See pages 5-6 and 11-18 of the specification.

[14]See pages 8-9 of the specification.

Nowhere does Buchmann et al. disclose the combination of a leukotriene B_4 receptor antagonist with a cyclooxygenase-2 **selective** inhibitor as required by the combination of claim 1. Buchmann et al.'s cyclooxygenase inhibitor is **not** stated to be a cyclooxygenase-2 selective inhibitor; nor is there any suggestion in the reference from which one skilled in the art might infer this. Buchmann et al. wholly fail to intimate anything whatsoever about selectivity for cyclooxygenase-2, the desirability thereof, or criteria for identifying it. As stated in MPEP 2131, "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, described in a single prior art reference."[15] (emphasis added).

While Buchmann et al. do not expressly disclose the required Cox-2 selectivity of claim 1, the Office states there is anticipation nonetheless because Buchmann et al.'s compounds "share a reasonably close correlation to the structures that are taught in Applicants' disclosure." This conclusion is untenable because Buchmann et al. do not disclose any particular inhibitors. So there is no structure, formula, or compound to correlate to applicants' structures. Buchmann et al. mention "cyclooxegenase inhibitors" at column 7, line 60 and in claim 10, but nowhere do they give an example of one. Accordingly, the basis of the rejection --- that Buchmann et al's inhibitors "share a reasonably close correlation to [applicants'] structures" — and hence the rejection itself, is invalid.

Moreover, as emphasized by the Board of Patent Appeals, "Anticipation of a claimed product cannot be predicated on mere conjecture as to the characteristics of a prior art product."[16] And as stated in MPEP 2112:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of

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[15] quoting Verdegaal Bros. v. Union Oil Co. of Calif., 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987). See MPEP §2131.

[16] Ex parte Standish, 10 USPQ2d 1454,1457 (Bd. Pat. App. & Int'f. 1988).

> conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

Because Buchmann et al. do not disclose every element of claim 1, and because conjecture and possibilities regarding Cox-2 selectivity do not cure this defect, the reference cannot fairly be deemed to anticipate claim 1.

Furthermore, the reference does not anticipate claim 1 because it is not enabling in that it does not describe any means by which to generate or confirm a **selective** cyclooxygenase-2 inhibitor. This is not surprising because Buchmann et al. state no concern about such selectivity or the desirability thereof. The Federal Circuit has stated that "even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985) citing *In re Borst*, 345 F.2d 851,855, 145 USPQ 554, 557 (CCPA 1965). While anticipation does not require the teaching in the prior reference to be in the exact words of the claimed subject matter, it does require sufficient enabling disclosure with respect to the entirety of the claimed invention, which is lacking in Buchmann et al.

Applicants respectfully take issue with the Office's reliance on the assertion that applicants have not set forth any evidence which would indicate that compounds in Buchmann et al. would not be selective cyclooxygenase-2 inhibitors. It would be impossible for the applicants to do so because Buchmann et al. did not list any inhibitor compounds. Moreover, the burden is not on the applicants to disprove whether such a characteristic is inherent. Rather, as stated in MPEP 2112, the burden is on the Office:

> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination

that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)

Applicants therefore respectfully request withdrawal of the rejection because Buchmann et al. make no reference to Cox-2 selectivity, the determination thereof, or the desirability thereof in any combination; and in fact Buchmann et al. list no cyclooxygenase inhibitor compounds, so there is no "basis in fact and/or technical reasoning to reasonably support" a conclusion as to Cox-2 selectivity.

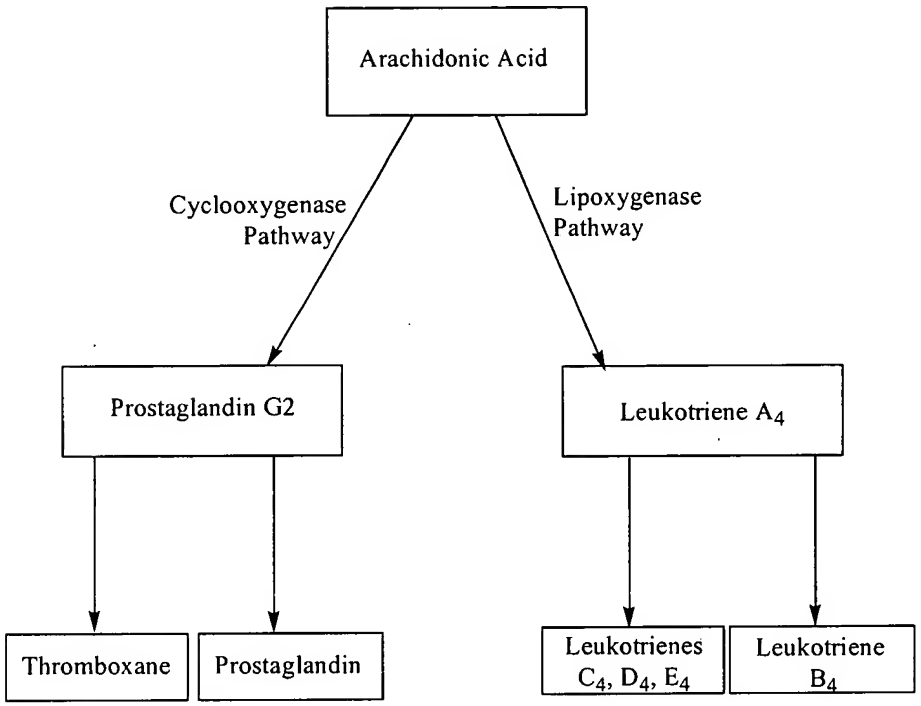
V. 35 U.S.C. §103 Rejection

Reconsideration is requested of the rejection of claims 1-4 and 6-9 under § 103(a) as obvious over Ducharme et al. and Rainsford.

According to the Office, Ducharme et al. teaches the substitution of cyclooxygenase-2 inhibitors for conventional NSAIDs in preparations where they are co-administered with other agents or ingredients. The Office states that Rainsford teaches the **leukotriene B_4 antagonist MK-866** can be co-administered with NSAIDs. Therefore, according to Office, the combined teachings of Ducharme et al. and Rainsford would teach a combination of Cox-2 inhibitors, substituted for NSAIDs, with leukotriene B_4 antagonists.

While Ducharme et al. do teach the substitution of cyclooxygenase-2 inhibitors for conventional NSAIDs in preparations where they are co-administered with other agents or ingredients, Rainsford **does not** teach that a **selective leukotriene B_4 antagonist** can be co-administered with NSAIDs. Instead, Rainsford examines the effects of indomethacin administration on the production of leukotriene C_4 in the efferent gastric circulation of pigs to establish if this cyclooxygenase inhibitor enhances the production of this 5-lipoxygenase (5-LO) product, and whether the **5-lipoxygenase inhibitor, MK-886**, inhibits the development of GI ulceration in rodents by NSAIDs.

Significantly, a selective leukotriene B_4 antagonist **is not the same** thing as a 5-lipoxygenase inhibitor such as MK-886. As detailed in the diagram below,[17] arachidonic acid may be oxygenated via either the cyclooxygenase pathway to produce prostaglandins or via the lipoxygenase pathway to produce leukotrienes.



Prostaglandin G2 and leukotriene A_4 are then converted into numerous other products, such as thromboxane, prostaglandins, or any of leukotrienes B_4, C_4, D_4, or E_4, which are direct mediators of numerous inflammatory responses.

The 5-LO inhibitor, MK-886, disclosed in Rainsford effectively inhibits the breakdown of arachidonic acid via the 5-LO mediated pathway before any compounds that elicit an immune response are produced. As a result, not only is leukotriene B_4 inhibited, but also are leukotriene A_4, leukotriene C_4, leukotriene D_4, and leukotriene E_4. However, the present claims affirmatively require that the leukotriene B_4 receptor antagonist be selective, i.e., selectively inhibit the production of **only** leukotriene B_4. It

[17]See, for example, Kuby, Janis, Immunology, 3rd edition (W.H. Freeman and Company, 1997) at page 368. A copy of this page is enclosed as Exhibit 1.

is possible that the Office was confused since MK-886 was erroneously included in claim 3 as a potential selective leukotriene B_4 antagonist. Claim 3 has been amended to remove MK-886.

As stated in MPEP 2143, obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion that the combination be made. The combination of Rainsford and Ducharme et al. is insufficient to teach the presently-claimed subject matter, because while Ducharme et al. teach the substitution of cyclooxygenase-2 inhibitors for conventional NSAIDs in preparations where they are co-administered with other agents or ingredients, Rainsford **does not** teach that a **selective leukotriene B_4 antagonist** can be co-administered with NSAIDs. Accordingly, the asserted combination of references does not render applicants' claims 1-4 and 6-9 obvious under 35 U.S.C. § 103(a).

VI. Non-statutory Double Patenting Rejection

Claims 1-4 and 6-9 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 6,136,839. On February 6, 2003, applicants filed a terminal disclaimer disclaiming the amount of any patent term on a patent issuing from this application which extends beyond the patent term of U.S. Patent No. 6,136,839 in order to obviate this rejection. In the terminal disclaimer, applicants clearly identify U.S. Patent No. 6,136,839 as the patent which forms the basis for the double patenting rejection. The Office contends, however, that applicants have not identified the application/patent which forms the basis for the double patenting rejection.

It appears the Office's sustained double patenting rejection is based upon the belief that applicants have misidentified the patent which forms the basis for the double patenting rejection as U.S. Patent No. 6,136,839. In the Office actions of both November 11, 2002 and June 14, 2003, the Office cites U.S. Patent No. 6,136,**830** as

the patent which forms the basis of the double patent rejection. U.S. Patent No. 6,136,**830**, titled "Sulphonyloxadiazolones and their use as microbicides," claims a process for preparing sulphonyloxadiazolones and their use as microbicides in crop protection.

The claims of the present application essentially are drawn to combinations of a selective cyclooxygenase-2 inhibitor and a selective leukotriene B_4 antagonist. The claims of U.S. Patent No. 6,136,**839** essentially are drawn to combinations of a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor. In some cases, applicants have claimed the same compounds for the combinations of the present application and U.S. Patent No. 6,136,839. Therefore, applicants are correct in identifying U.S. Patent No. 6,136,**839**, and not U.S. Patent No. 6,136,**830**, as the patent which forms the basis for the current double patenting rejection. Accordingly, applicants respectfully request reconsideration and withdrawal of the non-statutory double patenting rejection.

VII. New Claims 10-18

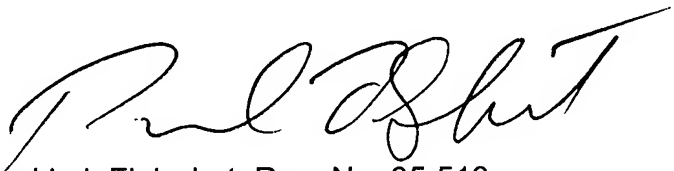
New claims 10-18 are directed to specific combinations of selective cyclooxygenase-2 inhibitors and selective leukotriene B_4 antagonists. Claim 10, 11, and 12 are patentable because the cited art fails to suggest the combination of a selective cyclooxygenase-2 inhibitor with the specifically listed selective leukotriene B_4 antagonist compounds. Claims 13, 14, and 15 are patentable because the cited art fails to suggest the combination of a specific single selective cyclooxygenase-2 inhibitor of each claim with the specifically listed selective leukotriene B_4 antagonist compounds. Claim 16 is patentable because the cited art fails to suggest the specific combination of the single inhibitor compound and single antagonist compound in the claim. Claims 17 and 18 are patentable because the cited art fails to suggest the specific combination of inhibitor and antagonist having the required selectivity.

VIII. Conclusion

In light of the foregoing, the Applicants request entry of the claim amendments, withdrawal of the claim rejections, and issuance of a Notice of Allowance of claims 1-18. The Examiner is invited to contact the undersigned attorney should any issues remain unresolved.

If there are any additional charges in this matter, please charge our Deposit Account No. 19-1345.

Respectfully submitted



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